Mutations in HIV-1 Reverse Transcriptase and Protease Associated with Drug Resistance

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INTRODUCTION

The knowledge of HIV-1 drug resistance continues to increase at an exponential rate. This is particularly true for resistance to HIV-1 protease inhibitors, for which the first resistant variants were described less than two years ago (Otto et al., *PNAS* **90**:7453–7457, 1993). Now resistance to virtually all classes of protease inhibitors has been documented. To keep our readership informed of newly described mutations, we have updated the tables below, which first appeared in IAVN in May 1994 (Vol 2; No 5). Following the tables is a list of abbreviations used. We hope that the tables' revised content will be useful to virologists and clinicians active in the field. We urge all investigators to provide additions or amendments of the table to any of the authors. Data formatted as in the table with an appropriate reference (abstract, manuscripts or paper) would be welcomed.

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NUCLEOSIDE RT INHIBITORS

Compound	Amino Acid Change	Codon Change	In Vitro	In Vivo	Comments	Confirmed by Site-directed Mutagenesis	Refs.
AZT	M41L	ATG to TTG	n.d	Yes	M41L: 4-fold resistance; M41L/T215Y:	Yes	[1, 2, 3]
	D67N	GAC to AAC	Yes	Yes	60- to 70-fold; K67N/K70R/T215Y/	Yes	
	K70R	AAA to AGA	Yes	Yes	K219Q: 120-fold; M41L/K67N/	Yes	
	T215Y	ACC to TAC	Yes	Yes	K70R/T215Y: 180-fold. Effect of	Yes	
	T215F	ACC to TTC	n.d.	Yes	T215Y is reversed by a ddI resis-	Yes	
	K219Q	AAA to CAA	n.d.	Yes	tance mutation (L74V), NNRTI	Yes	
	K219E	AAA to GAA	n.d.	No	mutations (L100I; Y181C) or a (-)-FTC/3TC mutation (M184V)	Yes	
ddI	L74V	TTA to GTA	No	Yes	5- to 10-fold resistance; cross-resistance to ddC; can reverse the effect of the T215Y AZT resistance mutation	Yes	[4]
	V75T	GTA to ACA	Yes	No	observed with D4T selection; cross-resistance to ddI/ddC	Yes	[5]
	M184V	ATG to GTG	Yes	Yes	3- to 4-fold resistance; cross-resistance to ddC	Yes	[6]
ddC	K65R	AAA to AGA	Yes	Yes	4- to 10-fold resistance; observed in pts on receving ddI or ddC therapy	Yes	[7, 8]
	T69D	ACT to GAT	No	Yes	5-fold resistance	Yes	[9]
	L74V	TTA to GTA			observed with ddI therapy	Yes	[2]
	V75T	GTA to ACA			observed with D4T selection in vitro	Yes	[4]
	M184V	ATG to GTG			observed with ddI, 3TC therapy	Yes	[6]
	Y215C	TTC to TGC	No	Yes	4-fold resistance; arises on background of T215YAZT resistance mutation	Yes	[10]
D4T	I50T	ATT to ACT	Yes	?	30-fold resistance	Yes	[11]
	V75T	GTA to ACA	Yes	Yes	7-fold resistance; cross-resistance to ddI, ddC, d4C, and (-)-FTC	Yes	[5]
3TC or (-)-FTC	M184V	ATG to GTG or GTA	Yes	Yes	>100-fold resistance; M184V and M184I can suppress effects of	Yes	[12–14]
	M184I	ATG to ATA	Yes	Yes	AZT resistance mutations	Yes	[12–14]
Foscarnet	W88S	TGG to TCG	No	Yes	4-fold resistance	Yes	[15]
	E89G	GAA to GGA	Yes	No	isolated by screening RT clones for ddGTP resistance; 14-fold viral resistance	Yes	[16]
	E89K	GAA to GGA	Yes	No	E89K and L92I cause increased		[17]
	L92I	TTA to ATA	Yes	No	susceptibility to AZT		[17]
	S156A	TCA to GCA	Yes	No	and HIV-1 specific RTI		[17]
	Q161L	CAA to CTA	Yes	Yes	10-fold resistance	Yes	[15]
	H208Y	CAT to TAT	Yes	Yes	2-fold resistance Q161L + H208Y cause increased susceptibiltity to AZT (100-fold), nevirapine (20-fold) and TIBO R82150 (30-fold)	Yes	[15]
1592U89	K65R	AAA to AGA	Yes	No	3-fold resistance	Yes	[18]
	L74V	TTA to GTA	Yes	No	4-fold resistance	Yes	
	Y115F	TAT to TTT	Yes	No	2-fold resistance	Yes	
	M184V	ATG to GTG	Yes	No	3-fold resistance K65R/M184V: 8-fold resistance L74V/M184V: 9-fold resistance L74V/Y115F/M184V: 11-fold resistance	Yes	

HIV-1-SPECIFIC RT INHIBITORS

Compound	Amino Acid Change	Codon Change	In Vitro	In Vivo	Comments	Confirmed by Site-directed Mutagenesis	Ref.
Nevirapine	A98G	GCA to GGA	No	Yes		Yes	[19]
	L100I	TTA to ATA	No	Yes		Yes	[20]
	K103N	AAA to AAC	No	Yes		Yes	[20]
	V106A	GTA to GCA	Yes	Yes	~100-fold resistance; no effect on AZT resistance	Yes	[19–22]
	V108I	GTA to ATA	No	Yes		Yes	[20]
	Y181C	TAT to TGT	Yes	Yes	>100-fold resistance; cross-resistance to other NNRTI; can suppress effects of AZT resistance mutations	Yes	[19, 23–25]
	Y181I	TGT to ATT	No	Yes	High-level resistance		[26]
	Y188C	TAT to TGT	No	Yes		Yes	[20]
	G190A	GGA to GCA	No	Yes		Yes	[19]
TIBO R82150	L100I	TTA to ATA	Yes	?	>100-fold resistance; can reverse effects of AZT resistance mutations	Yes	[27–29]
TIBO R82913	L100I	TTA to ATA	Yes	?		Yes	[21]
	K103N	AAA to AAC	Yes	?	>100-fold resistance	Yes	[22]
	V106A	GTA to GCA	Yes	?	~100-fold resistance	Yes	[21]
	E138K	GAG to AAG	Yes	?			[28]
	Y181C	TAT to TGT	Yes	?	>100-fold resistance	Yes	[21]
	Y188H	TAT to CAT	Yes	?		Yes	[28]
	Y188L	TAT to TTA	No	Yes		Yes	[30]
L′697,593	K103N	AAA to AAC	Yes	?	20-fold resistance	Yes	[23]
	Y181C	TAT to TGT	Yes	?	>100-fold resistance	Yes	[23]
L′697,661	A98G	GCA to GGA	No	Yes	8-fold resistance	Yes	[31]
	L100I	TTA to ATA	Yes	No	2-fold resistance	Yes	[31]
	K101E	AAA to GAA	No	Yes	8-fold resistance	Yes	[31]
	K103N	AAA to AAC	Yes	Yes	8-fold resistance	Yes	[31]
	K103Q	AAA to CAA	No	Yes	8-fold resistance	Yes	[32]
	V108I	GTA to GCA	Yes	Yes	4-fold resistance	Yes	[31]
	V179D	GTT to GAT	No	Yes	4-fold resistance	Yes	[31]
	V179E	GTT to GAG	No	Yes	8-fold resistance	Yes	[31]
	Y181C	TAT to TGT	Yes	Yes	>30-fold resistance	Yes	[31]
BHAP U-90152 (delaviridine)	P236L	CCT to CTT	Yes	?	P236L sensitizes RT ~10-fold to Nevirapine, TIBO R82193, and L′697,661	Yes	[33]
BHAP U-87201 (ateviridine)	K101E	AAA to GAA	No	Yes	K103N and Y181C observed with U-87201 monotherapy; K101E, Y188H, E233Y and K238T observed with U87201/AZT combination therapy		[34]
	K103N	AAA to AAC	No	Yes			[34]
	Y181C	TAT to TGT	No	Yes			[34]
	Y188H	TAT to CAT	No	Yes			[34]
	E233V	GAA to GTA	No	Yes			[34]
	P236L	CCT to CTT	Yes	No		Yes	[33]
	K238T	AAA to ACA	No	Yes			[34]
BHAP U 88204	L100I	TTA to ATA	Yes	?			[22, 35]
	V106A	GTA to GCA	Yes	?		Yes	[35]
	Y181C	TAT to TGT	Yes	?		Yes	[35]
	Y181I	TGT to ATT	Yes	Yes	High-level resistance to BHAP, Nevirapine, and TIBO. Observed in one Nevirapine-treated patient		[36]
HEPT	Y188C	TAT to TGT	Yes	?			[37]
E-EBU	Y181C	TAT to TGT	Yes	?			[37]
E-EBU-dM	Y106A	GTA to GCA	Yes	?			[37]

HIV-1-SPECIFIC RT INHIBITORS (cont.)

Compound	Amino Acid Change	Codon Change	In Vitro	In Vivo	Comments	Confirmed by Site-directed Mutagenesis	Ref.
E-EPU and	Y181C	TAT to TGT	Yes	?	Y188C is the predominant mutation	Yes	[38]
E-EPSeU	Y188C	TAT to TGT	Yes	?	for E-EPSeU; Y188C confers greater resistance to E-EPSeU/E-EPU than Y181C	Yes	[38]
α-APA R18893	Y181C	TAT to TGT	Yes	?		Yes	[39]
S-2720	G190E	GGA to GAA	Yes	?	Mutation decreases RT activity and viral replication competency	Yes	[40]
TSAO	E138K	GAG to AAG	Yes	?	$>$100-fold resistance	Yes	[41, 42]
BM+51.0836	Y181C	TAT to TGT	Yes	?		Yes	[43]

PROTEASE INHIBITORS

Compound	Amino Acid Change	Codon Change	In Vitro	In Vivo	Comments	Confirmed by Site-directed Mutagenesis	Refs.
A-77003	R8Q	CGA to CAA	Yes	?	10-fold viral resistance	Yes	[44, 45]
	R8K	CGA to AAA	Yes	?	10-fold viral resistance	Yes	[44]
	V32I	GTA to ATA	Yes	?	7-fold enzyme resistance	Yes	[45]
	M46I	ATG to ATA	Yes	?	No affect on susceptibility but restores replication kinetics of R8Q mutant	Yes	[44]
	M46L	ATG to TTG	Yes	?	2–3-fold enzyme resistance	Yes	[45]
	M46F	ATG to TTC	Yes	?	4-fold enzymee resistance	Yes	[45]
	G48V	GGG to GTG	Yes	?	R8K/M46I/G48V: 20-fold viral resistance		[46]
	V82I	GTC to ATC	Yes	?	no resistance alone but V32I and V82I are synergistic mutations yielding 20-fold enzyme resistance	Yes	[45]
	V82A	GTC to GCC	Yes	?	rare; seen with M46F		[47]
	I82T	ATC to ACC	Yes	?	G48V/I82Tcombined produce 100-fold viral resistance		[47]
A75925	V32I	GTA to ATA	Yes	?	40-fold viral resistance		[48]
ABT-538	V82F	GTC to TTC	Yes	?	V82F/I84V: 8- to 10-fold viral resistance	Yes	[49]
	I84V	ATA to GTA	Yes	?	M46I/L63P/A71V/V82F/I84V: 27-fold resistance	Yes	
BILA 1906 BS	V32I	GTA to ATA	Yes	?			[50]
	M46L	ATG to TTG	Yes	?	V32I/A71V: 3-fold viral resistance		
	A71V	GCT to GTT	Yes	?	V32I/A71V/M46I/I84V: 5-fold		
	I84V	ATA to GTA	Yes		V32I/A71V/M46I/I84V: 1000-fold (mutation also detected in p6/p7 cleavage site)		
BMS 186,318	A71T	GCT to ACT	Yes	?	A71T/V82A: 15-fold viral resistance;	Yes	[51]
	V82A		Yes	?	4-fold cross resistance to A77003	Yes	
L-735, 524	L10R	CTC? to CGC?	No	Yes	M46I/L63P/V82T: 4-fold viral resistance	Yes	[52]
	M46I	ATG to ATA	No	Yes	L10R/M46I/L63P/V82T: 4-fold viral resistance		
	L63P	CTC? to CCC?	No	Yes	L10R/M46I/L63P/V82T/I84V: 8-fold viral		
	V82T	GTC to ACC	No	Yes	resistance; cross resistance to XM-323 (15-		
	I84V	ATA to CTA	No	Yes	fold], A-80987 (4-fold), Ro-31-8959 (8-fold), VX-478 (8-fold), SC-52151 (8-fold)		
	V32I	GTA to ATA	Yes	?	V32I/M46L/V82A: 3-fold viral resistance		[46]
	M46I	ATG to ATA	Yes	?	V32I/M46L/A71V/V82A: 14-fold viral resistance		
	A71V	GCT to GTT	Yes	?			
	V82A	GTC to GCC	Yes	?			
P9941	V82A	GTC to GCC	Yes	?	6–8-fold resistance	Yes	[53]
Ro 31-8959	G48V	GGG to GTG	Yes	Yes		Yes	[54]
	I84V	ATA to GTA	Yes	?			[46]
	L90M	TTG to ATG	Yes	Yes	G48V/L90M combined yield >100-fold enzyme resistance, but double mutant rare in vivo; L90M most common in vivo		[54]
					G48V/I84V/L90M: 90-fold viral resistance		[46]
RPI-312	I84V	ATA to GTA	Yes	?	5-fold viral resistance	Yes	[55]
SC-52151	L24V	TTA to GTA	Yes	?	N88D: 10-fold viral resistance		[56, 57]
	G48V	GGG to GTG	Yes	?	G48V/V82A: 15-fold viral resistance		
	A71V	GCT to GTT	Yes	?	G48V/A71V/V75I/P81T: 20- to 30-fold		
	V75I	GTA to ATA	Yes	?	A71V/V75I/P81T: 30-fold viral resistance		
	P81T	CCT to ACT	Yes	?	L24V/G48V/A71V/V75I/P81T: 1000-fold		

PROTEASE INHIBITORS (cont.)

Compound	Amino Acid Change	Codon Change	In Vitro	In Vivo	Comments	Confirmed by Site-directed Mutagenesis	Refs.
	V82A	GTC to GCC	Yes	?	viral resistance; some cross resistance		
	N88D	AAT to GAT	Yes	?	to SC55389a and Ro31-8959, but not to L-735,524		
SC-55389	L10F	CTC to CGC	Yes	?	N88S seen alone with L10F;		[56, 57]
	N88S	AAT to AGT	Yes	?	10- to 20-fold viral resistance		
VB 11,328	L10F	CTC to GGC	Yes	?	L10F/I84V: 10-fold viral resistance		[58]
	M46I	ATG to ATA	Yes	?	I50V/M46I/I47V: 20-fold viral resiestance	Yes	[46, 58]
	I47V	ATA to CTA	Yes	?			
	I50V	ATT to GTT	Yes	?	3-fold viral resistance	Yes	[46]
	I84V	ATA to GTA	Yes	?			
XM323	L10F	CTC to CGC			L10F/V82A: 2.0-fold viral resistance;	Yes	[59]
	K45I	AAA to ATA			L10F/K45I/I84V: 50-fold		[46]
	G48V	GGG to GTG	Yes	?		Yes	[59]
	V82A	GTC to GCC	Yes	?	V82A/M46L: 7-fold resistance V82A/M46L/L97V: 11-fold resistance	Yes	[59]
	V82I	GTC to ATC	Yes	?	<2-fold viral resistance	Yes	[59]
	V82F	GTC to TTC	Yes	?	see below	Yes	[59]
	I84V	ATA to GTA	Yes	?	12-fold resistance alone; V82F/I84V: 92-fold resistance; cross resistant to P9941, but not A77003 or Ro 31-8959	Yes	[46, 59]
	L97V	TTA to GTA	Yes	?	no resistance alone; V82A/L97V: 3.0 fold resistance	Yes	[59]

ABBREVIATIONS

n.d.: not determined ?: unknown

Amino acids: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenyalanine; G, glycine, H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

1592U89:	(1S, 4R)-4-[2-amino-6-cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate
3TC:	(-)-β-L-2′,3′-dideoxy-3′-thiacytidine
α-APA 18893:	alpha-nitroanilino-phenylacetamide
A-77003:	C2 symmetry-based protease inhibitor (Abbott)
A-75925:	C2 symmetry-based protease inhibitor (Abbott)
ABT-538:	C2 symmetry-based protease inhibitor (Abbott)
BM+51.0836:	thiazolo-isoindolinone derivative
AzddU:	3′-azido-2′,3′-dideoxyuridine
AZT-p-DDI:	3′-azido-3′-deoxythymidilyl-(5′,5′)-2,3,-dideoxy-5′-inosinic acid
AZT:	3′-azido-2′,3′-dideoxythymidine
BHAP:	bisheteroarylpiperazine
BILA 1906:	protease inhibitor (Boehringer-Ingelheim)
BMS 186,318	aminodiol derivative HIV-1 protease inhibitor (Bristol-Myer-Squibb)
d4C:	2′,3′-didehydro, 2′,3′-deoxycytidine
d4T:	2′,3′-didehydro,3′-deoxythymidine
ddC:	2′,3′-dideoxycytidine
ddI	2′,3′-dideoxyinosine
EBU-dM:	5-ethyl-1-thioxymethyl-6-(3,5-dimethylbenzyl)-uracil
E-EBU:	5-ethyl-1-ethoxymethyl-6-benzyluracil
E-EPSeU:	1-(ethoxy-methyl)-(6-phenyl-selenyl)-5-ethyl-uracil
E-EPU:	1-(ethoxy-methyl)-(6-phenyl-thio)-5-ethyluracil
(-)-FTC:	(-)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiacytidine
HEPT:	1-[(2-hydroxyethoxy)methyl]6-(phenylthio)-thymine
L′697,593:	5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1H)-one
L′735,524:	hyrdoxyaminopentane amide HIV-1 protease inhibitor (Merck)
L′697,661:	3-{[(-4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one
L-FDDC:	(-)-β-L-5-fluoro-2′,3′-dideoxycytidine
L-FDDC:	(-)-β-L-5-fluoro-dioxolane cytosine
Nevirapine:	11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyridol[3,2-b;2′,3′-e] diazepin-6-one
NNRTI:	nonnucleoside reverse transcriptase inhibitor
P9941:	protease inhibitor (Dupont Merck); [2-pyridylacetyl-IIePheAIa-Ψ(CHOH)]2
PFA:	phosphonoformate (foscarnet)
PMEA:	9-(2-phosphonyl-methoxyethyl)adenine
Ro 31-8959:	hydroxyethylamine derivative HIV-1 protease inhibitor (Roche)
RPI-312:	peptidly protease inhibitor; 1-[(3s)-3-(N-alpha-benzyloxycarbonyl)-L-asparginyl) amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-proline amide
S-2720:	6-chloro-3,3-dimethyl-4-(isopropenyloxycarbonyl)-3,4,-dihydroquinoxalin-2(1H)thione
SC-52151	hydroxyethylurea isostere protease inhibitor (Searle)
SC-55389A	hydroxyethylurea isostere protease inhibitor (Searle)
TIBO R82150:	(+)-(5S)-4,5,6,7,-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]-benzo-diazepin-2(1H)-thione
TIBO 82913:	(+)-(5S)-4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1jk]-[1,4]benzodiazepin-2(1H)-thione
TSAO-m3T:	[2′,5′-bis-O-(tert-butyldimethylsilyl)-3′-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)]-b-d-pentofuranosyl-N3-methyl-thymine
U90152:	1-[3-[(1-methylethyl)-amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)-amino]-lH-indol-2yl] carbonyl]-piperazine
VB 11,382:	hydroxyethylsulphonamide protease inhibitor (Vertex)
VX-478:	hydroxyethyl-sulphonamide protease inhibitor (Vertex)
XM 323:	cyclic urea protease inhibitor (Dupont Merck)

Table 2 Combinations of HIV-1 RTase mutations that confer multi-drug resistance

RTase genotype	AZT	ddI	Nevirapine	3TC
Single drug resistance				
M41L/T215Y	R	S	S	S
L74V	S	R	Sensitive	S
Y181C or V106A	S	S	Resistant	S
Double drug resistance				
M41L/T215Y/L74V	R	R	S	S
M41L/T215Y/V106A	R	S	R	S
L74V/Y181C	S	R	R	S
M184V	S	R	S	R
Triple drug resistance				
M41L/T215Y/L74V/V106A	R	R	R	S
M41L/T215Y/L74V/V106A/M184V	S	R	R	R

From Larder, *J Fen Virol* **75**:951–957 (1994)

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